

WHAT IS CLAIMED IS:

1. A method for increasing the proliferative potential of a cardiomyocyte cell, comprising increasing the level of cyclin D2 activity in the 5 cardiomyocyte cell so as to increase the proliferative potential of the cardiomyocyte cell.
2. The method of claim 1, comprising:
providing cardiomyocyte cells in a culture medium;
10 introducing nucleic acid into the cardiomyocyte cells, said nucleic acid having a sequence of nucleotides encoding a cyclin D2 protein; and
culturing the cardiomyocyte cells under conditions suitable for expression of said cyclin D2 protein.
3. The method of claim 1, wherein said introduced nucleic acid has a nucleotide sequence corresponding to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or a nucleotide sequence having substantial identity thereto.
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4. The method of claim 3, wherein said introduced nucleic acid has a nucleotide sequence corresponding to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or said introduced nucleic acid hybridizes to nucleic acid having nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3 under stringent 20 conditions, and encodes a protein having cyclin D2 activity.
5. The method of claim 4, wherein said nucleotide sequence is operably linked to a promoter.
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6. The method of claim 4, wherein said promoter is a constitutive promoter.
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7. The method of claim 4, wherein said promoter is an inducible promoter.

8. The method of claim 4, wherein said promoter is a cardiomyocyte specific promoter.

5 9. The method of claim 1, wherein said cardiomyocyte cell is a mammalian cardiomyocyte cell.

10 10. A method for culturing cardiomyocyte cells, comprising:
providing cardiomyocyte cells in a culture medium, said cardiomyocyte
cells having an increased intracellular level of cyclin D2; and
culturing the cardiomyocyte cells in said culture medium.

15 11. The method of claim 10, wherein said cardiomyocyte cells have introduced nucleic acid encoding a cyclin D2 protein operably linked to a constitutive promoter.

12. The method of claim 10, wherein said cardiomyocyte cells have introduced nucleic acid encoding a cyclin D2 protein operably linked to an inducible promoter.

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13. The method of claim 10, wherein said cardiomyocyte cells have introduced nucleic acid encoding a cyclin D2 protein operably linked to a cardiomyocyte specific promoter.

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14. The method of claim 10, wherein said introduced nucleic acid is DNA having a nucleotide sequence corresponding to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or a nucleotide sequence having substantial identity thereto.

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15. The method of claim 10, wherein said introduced nucleic acid encodes a protein having the amino acid sequence of SEQ. I.D. NO. 2 or SEQ. I.D. NO. 4, or a polypeptide having an amino acid sequence at least 70% identical

to the amino acid sequence of SEQ. I.D. NO. 2 or SEQ. I.D. NO. 4, and which exhibits cyclin D2 activity.

16. The method of claim 10, wherein said culturing includes culturing
5 in the presence of a pharmacologic agent that induces an increase in the proliferative potential of the cells..

17. The method of claim 10, wherein said cardiomyocytes are
mammalian cardiomyocytes.

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18. The method of claim 10, wherein said cardiomyocytes are human
cardiomyocytes.

19. The method of claim 10, wherein said cardiomyocytes are murine
15 cardiomyocytes.

20. A cardiomyocyte cell having introduced nucleic acid encoding a
cyclin D2 protein.

20 21. The cell of claim 20, wherein said introduced nucleic acid has a
nucleotide sequence corresponding to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or
SEQ. I.D. NO. 3, or a nucleotide sequence having substantial identity thereto.

22. The cell of claim 21, wherein said introduced nucleic acid encodes
25 a polypeptide having the amino acid sequence of SEQ. I.D. NO. 2 or SEQ. I.D.
NO. 4, or a polypeptide having an amino acid sequence at least 70% identical to
the amino acid sequence of SEQ. I.D. NO. 2 or SEQ. I.D. NO. 4, and which
exhibits cyclin D2 activity.

30 23. The cell of claim 20, wherein said nucleotide sequence is operably
linked to a promoter.

24. The cell of claim 23, wherein said promoter is a constitutive promoter.

25. The cell of claim 23, wherein said promoter is an inducible
5 promoter.

26. The cell of claim 23, wherein said promoter is a cardiomyocyte specific promoter.

10 27. The cell of claim 20, wherein said cardiomyocyte cell is a mammalian cardiomyocyte cell.

28. The cell of claim 20, wherein said cardiomyocyte cell is a human cardiomyocyte cell.

15 29. A nucleic acid construct having a sequence of nucleotides encoding a cyclin D2 protein, said sequence of nucleotides operably linked to an inducible promoter.

20 30. The construct of claim 29, wherein said sequence of nucleotides corresponds to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or is a sequence of nucleotides having substantial identity thereto.

25 31. The construct of claim 29, wherein said sequence of nucleotides corresponds to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or is a sequence of nucleotides which hybridizes to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3 under stringent conditions and which encodes a polypeptide having cyclin D2 activity.

30 32. A nucleic acid construct having a sequence of nucleotides encoding a cyclin D2 protein operably linked to a cardiomyocyte-specific promoter.

33. The construct of claim 32, wherein said sequence of nucleotides corresponds to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or is a sequence of nucleotides having substantial identity thereto.

5 34. The construct of claim 32, wherein said sequence of nucleotides corresponds to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3, or is a sequence of nucleotides which hybridizes to nucleotides 4 to 870 of SEQ. I.D. NO. 1 or SEQ. I.D. NO. 3 under stringent conditions and which encodes a protein having cyclin D2 activity.

10 35. A method for increase the proliferative potential of myocardial cells in a mammal, comprising:

increasing the level of cyclin D2 in cardiomyocytes in myocardial tissue of the mammal so as to increase the proliferative potential of the cardiomyocytes.

15 36. The method of claim 35, which comprises transfecting said cardiomyocytes with an expression vector having nucleic acid encoding a cyclin D2 protein operably linked to a promoter.

20 37. The method of claim 36, wherein said promoter is a constitutive promoter.

38. The method of claim 36, wherein said promoter is an inducible promoter.

25 39. The method of claim 36, wherein said promoter is a cardiomyocyte specific promoter.

30 40. The method of claim 35, also comprising administering to the mammal an agent that increases activation of the cell cycle in the transfected cardiomyocytes.

41. The method of claim 40, wherein the pharmacologic agent is an adrenergic receptor agonist.

42. The method of claim 41, wherein the receptor agonist is a β -
5 adrenergic receptor agonist.

43. A method for providing proliferative cardiomyocytes in a mammal,
comprising:

10 providing cardiomyocytes in a mammal, said cardiomyocytes responsive
to an agent to increase the proliferative capacity of said cardiomyocytes; and
administering said agent to the mammal so as to increase the proliferative
capacity of the cardiomyocytes.

44. The method of claim 43, wherein said cardiomyocytes contain
15 introduced DNA encoding a cyclin D2 protein.

45. The method of claim 44, wherein said introduced DNA is
operatively linked to an inducible promoter, and said agent causes induction of
said inducible promoter.

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46. A transgenic, non-human mammal having cardiomyocytes
expressing introduced DNA encoding a cyclin D2 protein, the cardiomyocytes
thereby exhibiting an activated cell cycle.

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47. A modified D-type cyclin protein having removed therefrom one or
more phosphorylation sites present in its native form, the modified D-type cyclin
exhibiting the capacity to provide to mammalian cardiomyocytes an increased
proliferative potential and sustained DNA synthesis when subjected to injurious
stimuli.

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48. A nucleic acid molecule encoding a modified D-type cyclin of
claim